CAS ONLINE PRINTOUT

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     (FILE 'HOME' ENTERED AT 10:10:20 ON 17 APR 2002)

     FILE 'REGISTRY' ENTERED AT 10:11:15 ON 17 APR 2002
               E TRAMADOL/CN
L1           4 S E3-E5,E6

     FILE 'CAPLUS' ENTERED AT 10:12:14 ON 17 APR 2002

=> s l1
L2         566 L1

=> s oral
L3      144951 ORAL

=> s l3 and l2
L4         102 L3 AND L2

=> d bib kwic 95-102 l4

L4   ANSWER 95 OF 102  CAPLUS  COPYRIGHT 2002 ACS
AN   1993:27477  CAPLUS
DN   118:27477
TI   Antipyretic, analgesic and anti-inflammatory preparations
IN   Takahashi, Kazuhiko; Uji, Kingo; Takano, Akiko; Matsumoto, Koichi;
     Takahashi, Koichi
PA   Nippon Surfactant Kogyo K. K., Japan
SO   Jpn. Kokai Tokkyo Koho, 14 pp.
     CODEN: JKXXAF
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   JP 04217925        A2   19920807       JP 1991-85934    19910327
PRAI JP 1990-75575           19900327
IT   Pharmaceutical dosage forms
        (oral, of antipyretics and anti-inflammatories, polar lipids
        and polyhydric alcs. in)
IT   50-78-2, Aspirin   53-86-1, Indomethacin   54-21-7, Sodium salicylate
     61-68-7, Mefenamic acid   68-89-3, Sulpyrine   92-24-0, Naphthacene
     127-48-0, Trimethin   132-69-4, Benzydamine hydrochloride   379-79-3,
     Ergotamine tartrate   471-53-4, Glycyrrhetinic acid   530-78-9, Flufenamic
     acid   552-94-3, Salicyl salicylate   2016-36-6   2139-25-5, Perisoxal
     citrate   4394-00-7, Niflumic acid   5104-49-4, Flurbiprofen   13115-40-7,
     Dimethothiazine mesylate   13993-65-2, Methiazinic acid   15307-79-6,
     Diclofenac sodium   15687-27-1   17737-65-4, Clonixin   18046-21-4,
     Fentiazac   20187-55-7, Bendazac   22071-15-4   22131-79-9, Alclofenac
     25913-34-2   34148-01-1, Clidanac   34597-40-5, Fenoprofen calcium
     35941-71-0, Tiaramide hydrochloride 36282-47-0, Tramadol
     hydrochloride   36322-90-4, Piroxicam   36330-85-5, Fenbufen   38194-50-2,
     Sulindac   52549-17-4, Pranoprofen   54323-85-2, Prothizinic acid
     62952-06-1
     RL: BIOL (Biological study)
        (Antipyretic and anti-inflammatory prepns. contg., polar lipids and
        polyhydric alcs. in)

L4   ANSWER 96 OF 102  CAPLUS  COPYRIGHT 2002 ACS
AN   1992:120745  CAPLUS
DN   116:120745
TI   Opioid and nonopioid components independently contribute to the mechanism
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of action of tramadol, an 'atypical' opioid analgesic
AU Raffa, Robert B.; Friderichs, Elmar; Reimann, Wolfgang; Shank, Richard P.; Codd, Ellen E.; Vaught, Jeffry L.
CS R. W. Johnson Pharm. Res. Inst., Spring House, PA, 19477-0776, USA
SO J. Pharmacol. Exp. Ther. (1992), 260(1), 275-85
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB Tramadol hydrochloride produced dose-related antinociception in mouse abdominal constriction [ED50 = 1.9 (1.2-2.6) mg/kg i.p.], hot-plate [48.degree., ED50 = 21.4 (18.4-25.3) mg/kg s.c.; 55.degree., ED50 = 33.1 (28.2-39.1) mg/kg s.c.] and tail-flick [ED50 = 22.8 (10.2-30.1) mg/kg s.c.] tests. Tramadol also displayed antinociceptive activity in the rat air-induced abdominal constriction [ED50 = 1.7 (0.7-3.2) mg/kg **oral**] and hot-plate [51.degree., ED50 = 19.5 (10.3-27.5) mg/kg i.p.] tests. The antinociceptive activity of tramadol in the mouse tail-flick test was completely antagonized by naloxone, suggesting an opioid mechanism of action. Consistent with this, tramadol bound with modest affinity to opioid .mu. receptors and with weak affinity to .delta. and .kappa. receptors, with Ki values of 2.1, 57.6 and 42.7 .mu.M, resp. The pA2 value for naloxone obtained with tramadol in the mouse tail-flick test was 7.76 and was different from that obtained with morphine (7.94). In CXBK mice, tramadol, like morphine, was devoid of antinociceptive activity after intracerebroventricular administration, suggesting that the opioid component of tramadol-induced antinociception is mediated by the .mu.-opioid receptor. In contrast to the mouse tail-flick test and unlike morphine or codeine, tramadol-induced antinociception in the mouse abdominal constriction, mouse hot-plate (48.degree. or 55.degree.) or rat hot-plate tests was only partially antagonized by naloxone, implicating a nonopioid component. Further examn. of the neurochem. profile of tramadol revealed that, unlike morphine, it also inhibited the uptake of norepinephrine (Ki = 0.79 .mu.M) and serotonin (0.99 .mu.M). The possibility that this addnl. activity contributes to the antinociceptive activity of tramadol was supported by the finding that systemically administered yohimbine or ritanserin blocked the antinociception produced by intrathecal administration of tramadol, but not morphine, in the rat tail-flick test. These results suggest that tramadol-induced antinociception is mediated by opioid (.mu.) and nonopioid (inhibition of monoamine uptake) mechanisms. This hypothesis is consistent with the clin. experience of a wide sepn. between analgesia and typical opioid side effects.
IT **27203-92-5**, Tramadol
RL: BIOL (Biological study)
(analgesia from, opioid and nonopioid mechanism of)

L4 ANSWER 97 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1988:31750 CAPLUS
DN 108:31750
TI The antinociceptive activity of flupirtine: a structurally new analgesic
AU Nickel, B.
CS Biol. Res. Pharmacol., Homburg Degussa Pharma Gruppe, Frankfurt, D-6000/1, Fed. Rep. Ger.
SO Postgrad. Med. J., Suppl. (1987), 63(3), 19-28
CODEN: PMESAJ; ISSN: 0370-0593
DT Journal
LA English
AB In the electrostimulated pain test in mice the **oral** ED50 for flupirtine was 25.7 mg/kg. Thus, flupirtine was .apprx.31.7 times more potent than paracetamol and as potent as pentazocine. Morphine was 1.5 times and buprenorphine 9.9 times more potent than flupirtine. In the hot plate test in mice, flupirtine (ED50: 32 mg/kg) was .apprx.1/2 as potent as morphine. The **oral** and i.v. antinociceptive activity of

flupirtine in the elec. tooth pulp stimulation test in conscious dogs was 3.5 mg/kg, orally, and 0.7 mg/kg, i.v., which was similar to that of pentazocine. Buprenorphine had, as expected, stronger antinociceptive activity. Fifteen min after **oral** administration of 40 mg flupirtine/kg, the pain threshold in the electrostimulated pain test was increased by 54%. The maximal antinociceptive effect was obsd. 30 min after dosing. The analgesia lasted .gtoreq.75 min. Codeine elevated the pain threshold 15 min after dosing. Its maximal effect was also reached 30 min after application, but the antinociceptive activity wore off earlier than after flupirtine. The intracerebroventricular and intrathecal administration of flupirtine also caused dose-dependent analgesia in dose ranges which, when applied systemically, did not produced analgesica in rats. The antinociceptive activity of flupirtine was not abolished by naloxone whether given orally or by the intraventricular or intrathecal routes. In opiate receptor binding studies flupiritine had no affinity for .mu.-, .delta.-, or .kappa.-opiate receptors of the highest concn. used (10-5M). Whereas buprenorphine and tramadol showed a striking similarity in the pharmaco-EEG recorded from different parts of the brain (frontal cortex, thalamus, striatum and the mesencephalic reticular formation) of the freely moving rat, flupirtine was clearly different in action. It produced dose-dependent increases in nearly all frequency bands, but its effects were different from those of the minor tranquilizer diazepam and the anticonvulsant phenobarbital. Apparently, the central antinociceptive activity of flupirtine is not based on an opiate mechanism and is not comparable with that of diazepam and phenobarbital.

IT 50-06-6, Phenobarbital, biological studies 57-27-2, Morphine, biological studies 76-57-3, Codeine 103-90-2 359-83-1, Pentazocine 439-14-5, Diazepam **27203-92-5** 52485-79-7
RL: BIOL (Biological study)
(analgesia from flupirtine and)

L4 ANSWER 98 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1986:558715 CAPLUS
DN 105:158715
TI Bioavailability of enteral tramadol formulations. 1st Communication: Capsules
AU Lintz, W.; Barth, H.; Osterloh, G.; Schmidt-Boethelt, E.
CS Cent. Res., Gruenenthal G.m.b.H., Aachen, D-5100, Fed. Rep. Ger.
SO Arzneim.-Forsch. (1986), 36(8), 1278-83
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
AB After **oral** administration of Tramal capsules, thd active ingredient tramadol-HCl (I-HCl) **[36282-47-0]** was rapidly absorbed and its extent of absorption was higher than that of other analgesics as shown by bioavailability studies in humans. The abs. bioavailability of I was 68% and the area under the time-concn. curves were 2488 and 3709 ng h/mL after **oral** and i.v. administration, resp. Peak serum concn. of 280 ng/mL was reached 2 h after **oral** administration of 2 Tramal capsules. A serum concn. of 100 ng/mL (assumed as the threshold value of analgesic efficacy) was reached after 0.68 h and was maintained for 9 h. The half-life of absorption was 0.38 and the lag-time 0.48 h. In the terminal phase the biol. half-lives of I were 5.1 and 5.2 h after **oral** and i.v. administration, resp.

IT **36282-47-0**
RL: PROC (Process)
(bioavailability of, from capsules in humans)

L4 ANSWER 99 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1985:547172 CAPLUS
DN 103:147172

CAS ONLINE PRINTOUT

TI Drug delivery device
IN Bondi, Joseph V.
PA Merck and Co., Inc. , USA
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 147780	A2	19850710	EP 1984-115782	19841219
	EP 147780	A3	19870311		
	R: CH, DE, FR, GB, IT, LI, NL				
	JP 60158109	A2	19850819	JP 1984-274974	19841228
PRAI	US 1984-567835		19840103		

AB A delivery system for **oral** ingestion and rectal or vaginal insertion for delivery of a drug comprises a core (the active agent), poly(vinyl alc.) (I) [9002-89-5] film for coating of granules, suppositories, or tablets, or matrix for controlled release, and optionally a buffer I is used at 1-15% by wt. of the drug delivery system and the active agent 0.1-500 mg/dosage unit. Thus, a core tablet contained microcryst. cellulose 150, L-dopa [59-92-7] 250, and Mg stearate 2 mg, and the film coating soln. contained I super-hydrolyzed 2 parts and water 98 parts.

IT 50-02-2 50-03-3 50-04-4 50-23-7 50-24-8 50-28-2, biological studies 50-33-9, biological studies 50-48-6 50-53-3, biological studies 52-01-7 53-86-1 55-63-0 57-83-0, biological studies 57-92-1, biological studies 58-15-1 58-22-0 58-32-2 58-55-9, biological studies 58-74-2 58-93-5 58-94-6 59-92-7, biological studies 60-54-8 61-24-5 61-32-5 61-33-6, biological studies 71-27-2 78-11-5 84-04-8 87-33-2 93-14-1 114-07-8 124-94-7 154-21-2 302-25-0 303-53-7 318-98-9 378-44-9 438-41-5 439-14-5 477-30-5 479-18-5 514-36-3 523-87-5 525-66-6 555-30-6 1134-47-0 1225-55-4 1229-29-4 1406-05-9 1665-48-1 2152-44-5 4205-90-7 4697-36-3 5667-46-9 6202-23-9 7297-25-8 13655-52-2 14556-46-8 14663-23-1 15687-27-1 15825-70-4 16110-51-3 17692-38-5 21593-23-7 22204-53-1 22494-42-4 23031-32-5 24209-51-6 24358-76-7 25953-19-9 26839-75-8 26921-17-5 **27203-92-5** 28860-95-9 31879-05-7 35607-66-0 38194-50-2 56796-20-4 57524-89-7 98113-08-7
RL: BIOL (Biological study)
(controlled-release, poly(vinyl alc.) film coating for)

L4 ANSWER 100 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1982:62523 CAPLUS
DN 96:62523
TI Metabolism of tramadol in man and animal
AU Lintz, W.; Erlacin, S.; Frankus, E.; Uragg, H.
CS Abt. Pharmakokinet., Gruenenthal G.m.b.H., Aachen, 5100, Fed. Rep. Ger.
SO Arzneim.-Forsch. (1981), 31(11), 1932-43
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA German
AB Following the **oral** administration of 14C-labeled tramadol (I) [**27203-92-5**] to mice, hamsters, rats, guinea pigs, rabbits, dogs, and man, the metabolic pathways were investigated and the results compared. In all species the main metab. pathways are N- and O-demethylation (phase I reactions) and conjugation of O-demethylated compds. (phase II reactions). Eleven metabolites are known, 5 arising by phase I reactions and 6 by phase II reactions (glucuronides and sulfates). The 5 phase I metabolites are mono-O-demethyltramadol (II) [80456-81-1], mono-N-demethyltramadol (III) [80467-99-8], di-N-demethyltramadol (IV)

[80468-00-4], tri-N,O-demethyltramadol (V) [80468-01-5] and di-N,O-demethyltramadol (VI) [80468-02-6]. The biotransformation scheme of tramadol is qual. identical in man, dog, rabbit, guinea pig, rat, hamster, and mouse. In all species II and II-conjugates, VI and VI-conjugates, and III are the main metabolites, whereas IV, V, and V-conjugates were only formed in minor quantities. Following **oral** administration to man and animals I-14C was rapidly and almost completely absorbed. The unchanged drug and the metabolites are mainly excreted via kidneys. The cumulative renal excretion of total radioactivity accounts for approx. 90% in man and varies from 86-100% in mouse, hamster, rat, guinea pig, rabbit and dog; the residual of the applied radioactivity appears in the feces. Apparently, I is metabolized much more rapidly in animals than in man. For that reason there are appreciable differences between man and animals in the amt.of I excreted unchanged in the urine (about 30% and 1% of the **oral** dose, resp.). After incubation with .beta.-glucuronidase and arylsulfatase at least 81% of the excreted radioactivity could be extd. from the urine of man and animals (with the exception of the guinea pig and the rabbit). In man all extractable metabolites were identified.

IT **27203-92-5 36282-47-0**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, in humans and lab. animals)

L4 ANSWER 101 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1978:115344 CAPLUS
DN 88:115344
TI Toxicological study on tramadol, a new analgetic agent
AU Lagler, F.; Helm, F.; Etzel, V.; Kiel, H.
CS Toxikol. Pathol. Abt., Gruenenthal G.m.b.H., Aachen, Ger.
SO Arzneim.-Forsch. (1978), 28(1A), 164-72
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA German
AB After single **oral** administration of tramadol (I) [**27203-92-5**] to mice, rats, guinea pigs, rabbits, and dogs, the LD50 values were 350, 228, 850, 500, and 450 mg/kg, resp.; s.c. LD50 values in mice, rats, and guinea pigs were 200, 286, and 245 mg/kg, resp.; i.v. LD50 values in mice, rabbits, and dogs were 68, 40-50, and 50 mg/kg, resp. Newborn rats were 2-3 times more sensitive to I than adult animals. Toxic manifestations included decreased spontaneous activity, ataxia, salivation, vomiting, pupil dilation, exophthalmos, tremor, convulsions, and dyspnea. No sex differences in the reaction to I was obsd. Clin., hematol., clinicochem., and histol. investigations revealed no drug-related changes following repeated **oral** or parenteral administration of therapeutically EDs for 6 and 26 wk in rats and dogs or **oral** administration for 12 mo to dogs. I was well-tolerated locally after single or repeated parenteral administration. The drug had no mutagenic effect.

IT **27203-92-5**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of)

L4 ANSWER 102 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1978:115342 CAPLUS
DN 88:115342
TI Pharmacological studies on analgesia, dependence on and tolerance of tramadol, a potent analgetic drug
AU Friderichs, E.; Felgenhauer, F.; Jongschaap, P.; Osterloh, G.
CS Pharmakol. Abt., Gruenenthal G.m.b.H., Aachen, Ger.
SO Arzneim.-Forsch. (1978), 28(1A), 122-34
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal

CAS ONLINE PRINTOUT

LA German
AB In expts. on mice, rats, and rabbits, tramadol (I) [**27203-92-5**] had analgesic effects comparable with those of other strong narcotic-type analgesics. Orally I was as potent as codeine and dextropropoxyphene, but up to 4 times less potent than morphine. I was equally potent following s.c. or i.p. injection. Max. analgesia was reached 0.5-1 h after **oral** administration or 15-30 min after the i.p. route. Analgesia lasted 90-110 min. I was effective against both pain perception and the emotional component of pain. I analgesia was almost completely antagonized by pretreatment with morphine antagonists like nalorphine. I had additive effects when combined with morphine or its agonists. I also had antitussive activity. I had only a min. dependence liability and only min. tolerance to analgesia developed after long-term application.
IT **27203-92-5**
RL: BIOL (Biological study)
(analgesia from)

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CAS ONLINE PRINTOUT

=> d bib kwic 80-94 l4

L4 ANSWER 80 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1997:79878 CAPLUS
DN 126:98761
TI The mechanism(s) of action and pharmacokinetics of tramadol hydrochloride
AU Raffa, R. B.; Nayak, R. K.; Liao, S.; Minn, F. L.
CS The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477-0776, USA
SO Rev. Contemp. Pharmacother. (1995), 6(10), 485-497
CODEN: RCPHFW; ISSN: 0954-8602
PB Marius Press
DT Journal; General Review
LA English
AB A review with 103 refs. Tramadol-HCl is a centrally acting, synthetic analgesic with a novel mechanism of action: complementary and synergistic interaction between inhibition of neuronal monamine reuptake and weak affinity for opioid receptors. This duality of action has prompted the classification of tramadol as a nontraditional centrally acting analgesic. In most animal models, the analgesic action of tramadol is attenuated, but not blocked, by naloxone. In a study in humans, the attenuation by naloxone was reported to be 30-35%, demonstrating that the nonopioid component enhances tramadol's analgesic action. The nonopioid mechanism is probably related to the ability of tramadol to enhance the release or inhibit the neuronal reuptake of 5-hydroxytryptamine (Ki = 0.99 .mu.M) or norepinephrine (Ki = 0.78 .mu.M). Tramadol is a racemic mixt. of 2 pharmacol. active enantiomers. In vivo and in vitro studies suggest that each of these enantiomers independently contributes to antinociception and, together, they act in a complementary and synergistic manner. The synergy does not appear to extend to side-effect measures. Animal studies, clin. trials and epidemiol. data indicate minimal effect on heart rate, blood pressure or respiration, and minimal propensity for abuse. In clin. trials, tramadol has been found to have high **oral** abs. bioavailability (>70%) and low plasma-protein binding (.apprx.20%). It is extensively metabolized and is eliminated primarily via renal excretion. A metabolite, O-demethyltramadol, might contribute to its analgesic action. Based on the clin. analgesic efficacy of tramadol, the contribution of its nonopioid component and its epidemiol. history of minimal abuse liability, tramadol might be suitable for a wide variety of painful conditions and particularly appropriate for consideration for the treatment of persistent or chronic pain.
IT **27203-92-5**, Tramadol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mechanism(s) of action and pharmacokinetics of)

L4 ANSWER 81 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1996:696230 CAPLUS
DN 126:43
TI Pharmacology and clinical experience with tramadol in osteoarthritis
AU Katz, Warren A.
CS Presbyterian Medical Center, University Pennsylvania Health System, Philadelphia, PA, USA
SO Drugs (1996), 52(Suppl. 3), 39-47
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis
DT Journal; General Review
LA English
AB A review with 49 refs. Tramadol is a centrally acting analgesic that has been shown to be effective in a variety of acute and chronic pain states.

Unlike other centrally acting analgesics, it exerts a dual action by binding to the opioid receptor site in the central nervous system and by weakly inhibiting the reuptake of biogenic amines. Tramadol is rapidly and almost completely absorbed, with an onset of action occurring within 1 h of **oral** administration. The recommended dosage is 50 to 100mg every 4 to 6 h; however, regular administration is an alternative, particularly for chronic pain states such as osteoarthritis, where the use of the recently developed sustained release formulation may represent an important advantage. Published studies specifically evaluating the use of tramadol in this disease support its effectiveness. Nausea, drowsiness, constipation, dizziness, and sweating have been reported in assocn. with tramadol use. Nausea occurs early in the course of administration, and may be reduced by slowly titrating the dose of tramadol against response. Tramadol would appear to be particularly useful in the elderly population affected by osteoarthritis because, unlike nonsteroidal anti-inflammatory drugs, it does not aggravate hypertension or congestive heart failure, nor does it have the potential to cause peptic ulcer disease. Compared with narcotics, tramadol does not induce significant respiratory depression, constipation, or have significant abuse potential.

IT **27203-92-5**, Tramadol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacol. and clin. experience with tramadol in humans with osteoarthritis)

L4 ANSWER 82 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1996:437881 CAPLUS
DN 125:96076
TI Melt-extruded orally administrable sustained-release opioid formulations
IN Oshlack, Benjamin; Chasin, Mark; Huang, Hua-Pin; Sackler, David
PA Euro-Celtique, S.A., Luxembourg
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9614058	A1	19960517	WO 1995-US14745	19951103
	W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5965161	A	19991012	US 1994-334209	19941104
	CA 2204180	AA	19960517	CA 1995-2204180	19951103
	AU 9641570	A1	19960531	AU 1996-41570	19951103
	AU 705894	B2	19990603		
	EP 785775	A1	19970730	EP 1995-939928	19951103
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	HU 77626	A2	19980629	HU 1998-457	19951103
	JP 10508608	T2	19980825	JP 1995-515537	19951103
	IL 115871	A1	19990817	IL 1995-115871	19951103
	JP 3186064	B2	20010711	JP 1996-515537	19951103
	ZA 9509367	A	19960613	ZA 1995-9367	19951106
	TW 425288	B	20010311	TW 1996-85101623	19960209
	US 5958452	A	19990928	US 1997-833948	19970410
	US 2001033865	A1	20011025	US 1999-358828	19990722
	US 6335033	B2	20020101		

CAS ONLINE PRINTOUT

	US 6261599	B1	20010717	US 1999-360056	19990723
	AU 9947362	A1	19991028	AU 1999-47362	19990903
	US 2001036476	A1	20011101	US 2001-777616	20010206
PRAI	US 1994-334209	A2	19941104		
	AU 1996-41570	A3	19951103		
	WO 1995-US14745	W	19951103		
	US 1997-833948	A1	19970410		
	US 1999-360056	A1	19990723		

AB Bioavailable sustained-release **oral** opioid analgesic dosage forms, comprising a plurality of multiparticulates produced via melt extrusion techniques are disclosed. Sustained-release capsules contained morphine sulfate (I) 60, Eudragit RSPO 36, Eudragit L-100 6, and stearic acid 18 mg. The mean % I dissolved after 18 h was 95%.

IT 57-11-4, Stearic acid, biological studies 57-27-2, Morphine, biological studies 57-42-1, Meperidine 62-67-9, Nalorphine 64-39-1, Promedol 71-68-1, Hydromorphone hydrochloride 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 77-07-6, Levorphanol 77-14-5, Proheptazine 77-15-6, Ethoheptazine 77-20-3, Alphaprodine 77-94-1, Tributyl citrate 84-66-2, Diethyl phthalate 112-92-5, Stearyl alcohol 113-92-8, Chlorpheniramine maleate 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 127-35-5, Phenazocine 131-28-2, Narceine 143-52-2, Metopon 144-14-9, Anileridine 152-02-3, Levallorphan 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 427-00-9, Desomorphine 437-38-7, Fentanyl 441-61-2, Ethylmethylthiambutene 466-40-0, Isomethadone 466-97-7, Normorphine 466-99-9, Hydromorphone 467-18-5, Myrophine 467-83-4, Dipipanone 467-84-5, Phenadoxone 467-85-6, Normethadone 467-86-7, Dioxaphetyl butyrate 468-07-5, Phenomorphan 468-56-4, Hydroxypethidine 469-62-5, Propoxyphene 469-79-4, Ketobemidone 509-60-4, Dihydromorphine 509-78-4, Dimenoxadol 524-84-5, Dimethylthiambutene 545-90-4, Dimepheptanol 552-25-0, Diampromide 561-27-3, Heroin 561-48-8, Norpipanone 561-76-2, Properidine 562-26-5, Phenoperidine 639-48-5, Nicomorphine 911-65-9, Etonitazene 1531-12-0, Norlevorphanol 3572-80-3, Cyclazocine 3734-52-9, Metazocine 3861-76-5, Clonitazene 9004-57-3, Ethyl cellulose 10061-32-2 13495-09-5, Piminodine 14297-87-1, Benzyl morphine 15301-48-1, Bezitramide 15686-91-6, Propiram 20380-58-9, Tilidine 20594-83-6, Nalbuphine 25086-15-1, Eudragit l100 25384-17-2, Allylprodine **27203-92-5**, Tramadol **36282-47-0**, Tramadol hydrochloride 42408-82-2, Butorphanol 52485-79-7, Buprenorphine 53237-50-6 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7, Sufentanil 61380-40-3, Lofentanil 71195-58-9, Alfentanil 72522-13-5, Eptazocine 178806-87-6, Eudragit RSPO

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melt-extruded orally administrable sustained-release opioid formulations)

L4 ANSWER 83 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1996:399323 CAPLUS
DN 125:104127
TI High-performance liquid chromatographic determination of tramadol in human plasma
AU Nobilis, Milan; Pastera, Jiri; Anzenbacher, Pavel; Svoboda, Dalibor; Kopecky, Jiri; Perlik, Frantisek
CS Inst. Exp. Biopharm., Jt. Res. Cent. Acad. Sci. Czech Republic, Hradec Kralove, 500 02, Czech Rep.
SO J. Chromatogr., B: Biomed. Appl. (1996), 681(1), 177-183
CODEN: JCBBEP; ISSN: 0378-4347
DT Journal
LA English
AB Tramadol has been detd. in human plasma samples using a sensitive high-performance liq. chromatog. method. The plasma samples were extd.

with tert.-butylmethyl ether in one-step liq.-liq. extn. (recovery 86%) and analyses of the exts. were performed on reversed-phase silica gel using ion-pair chromatog. (verapamil as an internal std.) and fluorescence detection. The method was applied to the detn. of tramadol levels in twelve healthy volunteers after **oral** administration of 100 mg of tramadol in capsules of Protradon and Tramal.

IT **27203-92-5**, Tramadol
RL: ANT (Analyte); ANST (Analytical study)
(tramadol detn. in human plasma by HPLC)

L4 ANSWER 84 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1996:167253 CAPLUS
DN 124:278845
TI Dose-dependent time course of the analgesic effect of a sustained-release preparation of tramadol on experimental phasic and tonic pain
AU Thuerauf, N.; Fleischer, W. K.; Liefhold, J.; Schmid, O.; Kobal, G.
CS Department Experimental and Clinical Pharmacology and Toxicology, University Erlangen-Nurnberg, Erlangen, 91054, Germany
SO Br. J. Clin. Pharmacol. (1996), 41(2), 115-23
CODEN: BCPHBM; ISSN: 0306-5251
DT Journal
LA English
AB This study investigated the analgesic effect and its duration of a new sustained-release prepn. of tramadol in an exptl. pain model based on pain-related chemosomatosensory evoked potentials (CSSEPs) and subjective intensity ests. of painful phasic and tonic stimuli. Volunteers participated in a randomized, double-blind, 3-way crossover study. Measurements were obtained before and 0.5, 1, 4, 6, and 12 h after **oral** administration of the drug (100 or 200 mg) and placebo. CSSEPs were recorded after stimulation of 1 nostril with phasic, painful CO2 pulses. The other nostril was stimulated with a const. stream of dry air, which produced a tonic painful sensation. The subjects rated the perceived intensity of phasic and tonic stimuli via visual analog scales. In order to test for nonspecific effects, acoustic evoked potentials were recorded, the spontaneous EEG was analyzed in the frequency domain, the subject's vigilance was assessed in a tracking task, and the side effects of the drug were monitored. The sustained-release prepn. of tramadol produced a dose-related decrease in CSSEP amplitudes. The redn. in amplitudes outlasted the observation period of 12 h, demonstrating the prolonged duration of the analgesic effect. A dose-related decrease was obsd. for the ests. of tonic pain. Similarly to the decrease of amplitudes of the CSSEP, the redn. of the ratings of tonic pain outlasted the observation period of 12 h. The obsd. slight decrease in the ests. of phasic pain did not reach a statistically significant level when compared with placebo. No significant effect could be demonstrated for the perception of the phasic and the tonic pain as detd. by the McGill Questionnaire. A dose-related increase in the ests. of the side effects "drowsiness", "vertigo" and "sickness" but not for "tiredness" was demonstrated.

IT **27203-92-5**, Tramadol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(time course of the analgesic effect of a sustained-release prepn. of tramadol in humans)

L4 ANSWER 85 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1996:122427 CAPLUS
DN 124:220308
TI Contribution of monoaminergic modulation to the analgesic effect of tramadol
AU Desmeules, J. A.; Piguet, V.; Collart, L.; Dayer, P.
CS Division Clinical Pharmacology and Pain Clinic, Geneva University

Hospital, Geneva, CH-1211/14, Switz.
SO Br. J. Clin. Pharmacol. (1996), 41(1), 7-12
CODEN: BCPHBM; ISSN: 0306-5251
DT Journal
LA English
AB In humans, the central analgesic effect of tramadol 100 mg orally is only partially reversed by the opioid antagonist naloxone (0.8 mg i.v.). As suggested by in vitro and animal data tramadol analgesia may thus result from an action on opioid as well as monoaminergic pathways. The authors therefore investigated the effect of .alpha.2-adrenoceptor antagonism with yohimbine on tramadol analgesia. Healthy volunteers received tramadol (100 mg orally), followed (+3 h) by yohimbine (0.1 mg kg-1 i.v.), and yohimbine + naloxone (0.8 mg i.v.) and their resp. placebo according to a randomized, double-blind crossover, placebo (P) controlled design. Analgesia was assessed over 8 h by subjective pain threshold (pain intensity numerical scale-PINS) and objective pain threshold (RIII nociceptive reflex-RIII) monitoring. Tramadol induced a significant increase in both pain thresholds. Peak analgesic effect was obsd. at 3.7 h (RIII + 39.6% and PINS 50.1 .+-. s.e.mean 5%) and the analgesia lasted about 6 h. Yohimbine significantly reversed the analgesic effects of tramadol for 2.8 h with a max. decrease of 97% (RIII) and 67% (PINS), whereas the addn. of naloxone abolished tramadol effects throughout the study period with a decrease of 90% (RIII) and 79% (PINS). Yohimbine alone did not significantly reduce pain thresholds. .alpha.2-Adrenoceptor antagonism reverses tramadol effects, thus pointing to the significant role of monoaminergic modulation and the synergy with opioid agonism in tramadol antinociception after a single **oral** dose.
IT **27203-92-5**, Tramadol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(contribution of monoaminergic modulation to the analgesic effect of tramadol)

L4 ANSWER 86 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1995:774804 CAPLUS
DN 123:152926
TI Opioid formulations for treating pain
IN Sackler, Richard; Goldenheim, Paul; Kaiko, Robert
PA Euro-Celtique, S.A., Luxembourg
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9514460	A1	19950601	WO 1994-US13606	19941122
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5478577	A	19951226	US 1993-156468	19931123
AU 9513313	A1	19950613	AU 1995-13313	19941122
AU 693134	B2	19980625		
CN 1130352	A	19960904	CN 1994-192723	19941122
EP 731694	A1	19960918	EP 1995-904755	19941122
EP 731694	B1	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 73976	A2	19961028	HU 1995-3468	19941122

	JP 09505602	T2	19970603	JP 1994-515254	19941122
	EP 1023896	A2	20000802	EP 2000-107670	19941122
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	AT 212831	E	20020215	AT 1995-904755	19941122
	TW 420617	B	20010201	TW 1994-83111985	19941221
	FI 9505782	A	19960130	FI 1995-5782	19951201
	NO 9504925	A	19960523	NO 1995-4925	19951205
	US 5672360	A	19970930	US 1996-578688	19960722
	AU 9887145	A1	19981217	AU 1998-87145	19980925
	AU 735113	B2	20010628		
PRAI	US 1993-156468	A2	19931123		
	AU 1995-13313	A3	19941122		
	EP 1995-904755	A3	19941122		
	WO 1994-US13606	W	19941122		

AB Patients are treated with 24-h **oral** sustained-release opioid formulations which, upon administration, provide an initially rapid opioid absorption such that the min. effective analgesic concn. of the opioid is more quickly achieved. These sustained-release opioid formulations include at least one retardant material to cause the opioid analgesic to be released at such a rate as to provide an analgesic effect after **oral** administration to humans for at least 24 h, and are characterized by providing an absorption half-life of 1-8 h. Thus, hydromorphone beads were prepd. by dissoln. of hydromorphone-HCl in water and addn. of Opadry Y-5-1442 and mixing to get a suspension. The suspension was coated with an acrylic polymer and evaluated in humans.

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 62-67-9, Nalorphine 64-31-3, Morphine sulfate 64-39-1, Promedol 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, EthylMorphine 76-99-3, Methadone 77-07-6, Levorphanol 77-14-5, Proheptazine 77-15-6, Ethoheptazine 77-20-3, Alphaprodine 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 127-35-5, Phenazocine 131-28-2, Narceine 143-52-2, Metopon 144-14-9, Anileridine 152-02-3, Levallorphan 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 427-00-9, Desomorphine 441-61-2 466-40-0, Isomethadone 466-97-7, Normorphine 466-99-9, Hydromorphone 467-18-5, Myrophine 467-83-4, Dipipanone 467-84-5, Phenadoxone 467-85-6, Normethadone 467-86-7 468-07-5, Phenomorphan 468-56-4, Hydroxypethidine 469-62-5, Propoxyphene 469-79-4, Ketobemidone 509-60-4, Dihydromorphine 509-78-4, Dimenoxadol 524-84-5, Dimethylthiambutene 545-90-4, Dimepheptanol 552-25-0, Diampromide 561-27-3, Heroin 561-48-8, Norpipanone 561-76-2, Properidine 562-26-5, Phenoperidine 639-48-5, Nicomorphine 911-65-9, Etonitazene 1531-12-0, Norlevorphanol 3572-80-3, Cyclazocine 3734-52-9, Metazocine 3861-76-5 13495-09-5, Piminodine 14297-87-1, Benzylmorphine 15301-48-1, Bezitramide 15686-91-6, Propiram 20380-58-9, Tilidine 20594-83-6, Nalbuphine 25384-17-2, Allylprodine **27203-92-5**, Tramadol 42408-82-2, Butorphanol 52485-79-7, Buprenorphine 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7, Sufentanil 61380-40-3, Lofentanil 71195-58-9, Alfentanil 72522-13-5, Eptazocine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release opioid analgesic formulations evaluation in humans)

L4 ANSWER 87 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1995:760773 CAPLUS
DN 123:208624
TI Pharmacokinetics and relative bioavailability of tramadol hydrochloride tablet
AU Li, Hua; Wang, Ning; Qian, Jianzhong; Wang, Shufan; Wan, Hong
CS Res. Inst. Pharmacology Toxicology, Inst. Military Medical Sci., Beining, 100850, Peop. Rep. China
SO Zhongguo Linchuang Yaolixue Zazhi (1995), 11(1), 28-32

CAS ONLINE PRINTOUT

CODEN: ZLYZE9; ISSN: 1001-6821
DT Journal
LA Chinese
AB A single 100 mg **oral** dose of domestic tramadol tablets or imported tramadol capsules (Mabron) was given to 8 healthy male volunteers in randomized self-crossover study. Plasma concns. of tramadol were detd. by gas chromatog. The results suggested that domestic tramadol tablet was not significantly different from imported capsules.
IT **27203-92-5**, Tramadol **36282-47-0**, Tramadol hydrochloride
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics and bioavailability of tramadol hydrochloride tablet)

L4 ANSWER 88 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1995:252633 CAPLUS
DN 122:17258
TI Controlled-release formulation containing tramadol
IN Miller, Ronald Brown; Leslie, Stewart Thomas; Malkowska, Sandra Therese Antoi; Smith, Kevin John; Wimmer, Walter; Winkler, Horst; Hahn, Udo; Prater, Derek Allan
PA Euroceltique S.A., Luxembourg
SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 14

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 624366	A1	19941117	EP 1994-303128	19940429
	EP 624366	B1	19960529		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	DE 4315525	A1	19941117	DE 1993-4315525	19930510
	GB 2284760	A1	19950621	GB 1993-24045	19931123
	GB 2284760	B2	19980624		
	GB 2287880	A1	19951004	GB 1994-4928	19940314
	IL 109460	A1	19980310	IL 1994-109460	19940427
	ZA 9402959	A	19950105	ZA 1994-2959	19940428
	EP 699436	A1	19960306	EP 1995-114527	19940429
	EP 699436	B1	20010613		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	AT 138566	E	19960615	AT 1994-303128	19940429
	ES 2088312	T3	19960801	ES 1994-303128	19940429
	EP 729751	A1	19960904	EP 1996-101147	19940429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	ES 2159591	T3	20011016	ES 1995-114527	19940429
	CZ 288517	B6	20010711	CZ 1994-1093	19940504
	FI 9402092	A	19941111	FI 1994-2092	19940506
	HU 75703	A2	19970528	HU 1994-1478	19940506
	CA 2123160	AA	19941111	CA 1994-2123160	19940509
	NO 9401719	A	19941111	NO 1994-1719	19940509
	AU 9461963	A1	19941117	AU 1994-61963	19940509
	PL 176474	B1	19990630	PL 1994-303367	19940509
	PL 177332	B1	19991029	PL 1994-326373	19940509
	JP 07053361	A2	19950228	JP 1994-96671	19940510
	JP 3045924	B2	20000529		
	CN 1099262	A	19950301	CN 1994-105356	19940510
	US 5591452	A	19970107	US 1994-241129	19940510
	JP 11124327	A2	19990511	JP 1998-229718	19940510
	SK 279971	B6	19990611	SK 1994-541	19940510
	EP 654263	A1	19950524	EP 1994-308493	19941117
	EP 654263	B1	20020123		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

	AT 212224	E	20020215	AT 1994-308493	19941117
	FI 9405476	A	19950524	FI 1994-5476	19941122
	NO 9404473	A	19950524	NO 1994-4473	19941122
	HU 74910	A2	19970328	HU 1994-3353	19941122
	HU 217205	B	19991228		
	SK 280496	B6	20000313	SK 1994-1406	19941122
	PL 178883	B1	20000630	PL 1994-305939	19941122
	AU 9479015	A1	19950601	AU 1994-79015	19941123
	AU 682223	B2	19970925		
	ZA 9409296	A	19950808	ZA 1994-9296	19941123
	CN 1116521	A	19960214	CN 1994-118503	19941123
	JP 07196475	A2	19950801	JP 1994-289936	19941124
	ZA 9502013	A	19951211	ZA 1995-2103	19950310
	US 6326027	B1	20011204	US 1995-449772	19950524
	US 5849240	A	19981215	US 1996-607852	19960227
	US 5891471	A	19990406	US 1996-607851	19960227
	US 6254887	B1	20010703	US 1996-677798	19960710
	US 5879705	A	19990309	US 1997-843571	19970418
	US 5965163	A	19991012	US 1997-944106	19970930
	AU 9739957	A1	19971218	AU 1997-39957	19971007
	US 6143328	A	20001107	US 1999-264399	19990308
	CN 1240132	A	20000105	CN 1999-106642	19990517
	NO 9903484	A	19941111	NO 1999-3484	19990715
	US 6162467	A	20001219	US 1999-370270	19990809
	US 2001019725	A1	20010906	US 2000-740732	20001219
	US 2001036477	A1	20011101	US 2001-800204	20010306
	NO 2001003566	A	19941111	NO 2001-3566	20010719
PRAI	DE 1993-4315525	A	19930510		
	GB 1993-24045	A	19931123		
	GB 1994-4544	A	19940309		
	GB 1994-4928	A	19940314		
	GB 1993-15467	A	19930727		
	GB 1994-3922	A	19940301		
	EP 1994-303128	A3	19940429		
	EP 1995-114527	A3	19940429		
	JP 1994-96671	A3	19940510		
	US 1994-241129	A3	19940510		
	EP 1994-304144	A	19940609		
	GB 1994-11842	A	19940614		
	US 1994-269208	B1	19940630		
	US 1994-343630	A3	19941122		
	US 1996-677798	A1	19960710		
	US 1997-843571	A1	19970418		
	US 1997-944106	A1	19970930		
	US 1999-370270	A1	19990809		

AB A controlled-release prepn. for **oral** administration contains tramadol or a pharmaceutically acceptable salt thereof, as active ingredient. The controlled-release matrix comprises C1-6-alkyl cellulose, C12-36 aliph. alc., and optionally polyalkylene glycol. For example, a tablet contained tramadol.cntdot.HCl 100.0, lactose 58.0, Et cellulose 15.0, cetostearyl alc. 52.0, Mg stearate 2.0, and talc 3.0 mg.

IT **27203-92-5**, Tramadol **36282-47-0**, Tramadol hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release analgesic tablets)

L4 ANSWER 89 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1994:646064 CAPLUS
DN 121:246064
TI Muscle rigidity induced by the opioid analgesic tramadol, but not by the non-opioid flupirtine
AU Ossowska, Krystyna; Wolfarth, Stanislaw
CS Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31-343,

Pol.
SO Pol. J. Pharmacol. (1994), 46(1-2), 61-5
CODEN: PJPAE3; ISSN: 1230-6002
DT Journal
LA English
AB The effect of high doses of 2 analgesics, tramadol and flupirtine on the electromyog. activity in the gastrocnemius soleus muscles was examd. Tramadol (100-200 mg/kg **oral**) dose-dependently induced a tonic electromyog. activity, which is generally accepted as a model of the opiate-induced muscle rigidity. That effect was antagonized by i.p. injection of naloxone (0.8 mg/kg i.p.). On the other hand, flupirtine even in the high doses (100-200 mg/kg po) did not induce any tonic electromyog. activity. The results confirm an opiate-like action of tramadol, but not that of flupirtine, on the muscle tension.
IT **27203-92-5**, Tramadol 56995-20-1, Flupirtine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(muscle rigidity induction by opioid an not by nonopioid analgesics)

L4 ANSWER 90 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1994:620754 CAPLUS
DN 121:220754
TI The pharmacology of tramadol
AU Dayer, Pierre; Collart, Laurence; Desmeules, Jules
CS Div. Clin. Pharmacol., Univ. Hosp., Geneva, Switz.
SO Drugs (1994), 47(Suppl. 1), 3-7
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with many refs. (.+-.)-Tramadol is a central analgesic with low affinity for opioid receptors. The rate of prodn. of its M1 metabolite (O-demethyl tramadol) is influenced by debrisoquine-type polymorphism, and this metabolite shows a higher affinity for opioid receptors than the parent drug. Exptl. and clin. data suggest that tramadol may also exert its analgesic effect through direct modulation of central monoaminergic pathways. Indeed, after a single **oral** dose, the role of the .mu.-receptor agonist component of the antinociceptive effect of tramadol appears to be minor, with most of the analgesic effect being attributable to nonopioid properties of the parent compd. Approx. 2-fold accumulation of the parent compd. and the M1 metabolite may be expected during multiple dose treatment. The duration of analgesic effect after a single **oral** does of tramadol 100mg is about 6 h. Clin. experience has confirmed that tramadol is an effective and relatively safe analgesic that may be of value in several pain conditions not requiring treatment with strong opioids.
IT **27203-92-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, as analgesic, in humans and lab. animals)

L4 ANSWER 91 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1993:567731 CAPLUS
DN 119:167731
TI Solubilizing agent compositions for slightly soluble pharmaceuticals
IN Takahashi, Kazuhiko; Uji, Kingo; Niwa, Akiko; Matsumoto, Koichi; Takahashi, Koichi
PA Nihon Surfactant Kogyo Kk, Japan
SO Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 05178763	A2	19930720	JP 1991-45423	19910219

IT Pharmaceutical dosage forms
(**oral**, antipyretic and anti-inflammatory agents, contg. polyalc. fatty acid esters and oily substances as solubilizers)

IT 50-78-2, Aspirin 53-86-1, Indomethacin 54-21-7, Sodium salicylate 61-68-7, Mefenamic acid 68-89-3, Sulpyrine 69-72-7, Salicylic acid, biological studies 132-69-4, Benzydamine hydrochloride 379-79-3, Ergotamine tartrate 471-53-4, Glycyrrhetinic acid 530-78-9, Flufenamic acid 552-94-3, Salicylsalicylic acid 2016-36-6, Choline salicylate 2139-25-5, Perisoxal citrate 4394-00-7, Niflumic acid 5104-49-4, Flurbiprofen 13115-40-7, Dimethothiazine mesylate 13993-65-2, Metiazinic acid 15307-79-6, Diclofenac sodium 15687-27-1, Ibuprofen 17737-65-4, Clonixin 18046-21-4, Fentiazac 20187-55-7, Bendazac 22071-15-4, Ketoprofen 22131-79-9, Alclofenac 22204-53-1, Naproxen 25913-34-2, Tinoridine hydrochloride 34148-01-1, Clidanac 34597-40-5, Fenoprofen calcium 35711-34-3, Tolmetin sodium 35941-71-0, Tiaramide hydrochloride **36282-47-0**, Tramadol hydrochloride 36322-90-4, Piroxicam 36330-85-5, Fenbufen 38194-50-2, Sulindac 52549-17-4, Pranoprofen 54323-85-2, Protizinic acid 77337-52-1
RL: BIOL (Biological study)
(solubilizers for, polyalc. fatty acid esters and oily substances as)

L4 ANSWER 92 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1993:488442 CAPLUS
DN 119:88442
TI Analysis of tramadol and its metabolites in human urine
AU Xu, Y. X.; Xu, Y. Q.; Zhang, C. J.; Shen, L.
CS China Doping Control Cent., Natl. Res. Inst. Sports Med., Beijing, 100029, Peop. Rep. China
SO Yaoxue Xuebao (1993), 28(58), 379-83
CODEN: YHHPAL; ISSN: 0513-4870
DT Journal
LA Chinese
AB A GC-MS method for the anal. of tramadol and its 4 metabolites in human urine is described. The urine samples were acid hydrolyzed with hydrochloric acid, cleaned with di-Et ether and extd. with dichloromethane-isopropanol (9:1). After derivatization, the soln. was analyzed with GC-MSD. Tramadol and its 4 metabolites were detected in urine samples 2-40 h after **oral** administration. The recovery of tramadol was 85.2%, the detection limit was down to 12.5 pg. The derivatization methods are discussed.
IT **27203-92-5**, Tramadol **27203-92-5D**, Tramadol, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human urine by gas chromatog.-mass spectrometry)

L4 ANSWER 93 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1993:480214 CAPLUS
DN 119:80214
TI Analgesic compositions containing tramadol derivatives and opioids
IN Raffa, Robert B.; Vaught, Jeffrey L.
PA McNeilab, Inc., USA
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 534628	A1	19930331	EP 1992-308076	19920904
	EP 534628	B1	19961120		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

CA	2077637	AA	19930307	CA 1992-2077637	19920904
NO	9203453	A	19930308	NO 1992-3453	19920904
AU	9222185	A1	19930311	AU 1992-22185	19920904
AU	657351	B2	19950309		
HU	63556	A2	19930928	HU 1992-2845	19920904
HU	217584	B	20000228		
ZA	9206732	A	19940304	ZA 1992-6732	19920904
AT	145330	E	19961215	AT 1992-308076	19920904
ES	2096726	T3	19970316	ES 1992-308076	19920904
CN	1071835	A	19930512	CN 1992-111382	19920905
CN	1051705	B	20000426		
IL	103070	A1	19961016	IL 1992-103070	19920906
JP	06107540	A2	19940419	JP 1992-262693	19920907
JP	3244540	B2	20020107		
US	5468744	A	19951121	US 1994-268382	19940630
CN	1198929	A	19981118	CN 1998-107417	19980420
PRAI US	1991-755923	A	19910906		
	US 1992-976728	B1	19921116		

IT Pharmaceutical dosage forms
(**oral**, tramadol and opioids in, for treatment of pain)

IT 147831-11-6, Tramadol-codeine mixt. 147831-12-7, Tramadol-oxycodone mixt. 147831-13-8, Tramadol-hydrocodone mixt. **147928-89-0**, Tramadol hydrochloride-codeine phosphate mixt. 148133-67-9, Tramadol N-oxide-oxycodone mixt. 148133-68-0, O-Desmethyltramadol-hydrocodone mixt.
RL: BIOL (Biological study)
(analgesic compns. contg.)

IT **36282-47-0**, Tramadol hydrochloride
RL: PROC (Process)
(conversion of, to hydrate)

IT **27203-92-5**
RL: RCT (Reactant)
(oxidn. of)

L4 ANSWER 94 OF 102 CAPLUS COPYRIGHT 2002 ACS
AN 1993:246794 CAPLUS
DN 118:246794
TI Achiral and chiral high-performance liquid chromatographic determination of tramadol and its major metabolites in urine after **oral** administration of racemic tramadol
AU Elsing, B.; Blaschke, G.
CS Dep. Pharm. Chem., Univ. Muenster, Muenster, W-4400, Germany
SO J. Chromatogr., Biomed. Appl. (1993), 612(2), 223-30
CODEN: JCBADL; ISSN: 0378-4347
DT Journal
LA English
TI Achiral and chiral high-performance liquid chromatographic determination of tramadol and its major metabolites in urine after **oral** administration of racemic tramadol
AB A reversed-phase high-performance liq. chromatog. method for the simultaneous detn. of tramadol and its major metabolites O-demethyltramadol and N-demethyltramadol in urine has been developed. The detn. of the enantiomeric ratios of the three compds. was achieved using a Chiralpak AD column and a Chiralcel OD column, resp. After **oral** administration of racemic tramadol to five healthy volunteers, inter-individual differences of the excreted amts. and the enantiomeric ratios of the compds. were obsd.

IT **27203-92-5**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, chiral detn. in urine of humans in relation to)

CAS ONLINE PRINTOUT

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